PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Donald W. Kufe

Serial No.: 10/733,212

Filed: December 11, 2003

For: REGULATION OF CELL GROWTH BY MUC1

Confirmation No. 7998

Group Art Unit: 1633

Examiner: Hill, Kevin Kai

Atty. Dkt. No.: GENU:009USD1

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October 9, 2009 Monica De La Paz
Date Monica A. De La Paz

SUPPLEMENTAL APPEAL BRIEF

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APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-01450

Dear Sir:

Appellants hereby submit this Supplemental Appeal Brief to the Board of Patent Appeals and Interferences in response to the Notice of Non-Compliant Appeal Brief dated September 29, 2009, the final Office Action mailed on March 2, 2009, and the Advisory Action mailed on May 28, 2009. A Notice of Appeal was filed on July 1, 2009, bringing the initial deadline to file the appeal brief to September 1, 2009. Thus the appeal brief was timely filed on August 25, 2009.

It is believed that no fee is required for this filing. The Commissioner is hereby authorized to deduct any fees required under 37 C.F.R. §§ 1.16 to 1.21 in connection with the filing of this paper, from Fulbright & Jaworski Deposit Account No. 50-1212/GENU:009USD1.

I. Real Party in Interest

The real parties in interest are the assignee, the Dana Farber Cancer Institute, Boston, MA, and the licensee, Genus Oncology, LLC.

II. Related Appeals and Interferences

There are no related appeals or interferences.

III. Status of the Claims

Claims 1-8 were filed with the original application. The claims were subjected to a restriction requirement, and as a result, claims 2-4 and 6 were withdrawn. Thus, claims 1, 5, and 7-8 were examined. In an amendment filed with a response to the Office Action mailed on October 12, 2006, new claims 9-16 were added. Claims 10-12 and 14 were subsequently withdrawn per the Office Action mailed on June 12, 2007, and new claims 17-18 were added in an Amendment filed in response to this Office Action. New claims 19-27 were added in a Supplemental Amendment and Response to Office Action mailed on June 12, 2007. Claims 20-21 and 27 were canceled in an Amendment filed with a Response to the Final Office Action mailed on March 2, 2009. Thus, the claims currently under consideration, which are the subject of this appeal, include claims 1, 5, 7-9, 13, 15-17, 19, and 22-26. The pending claims are attached in Appendix A.

IV. Status of the Amendments

The amendments offered following mailing the final Office Action were entered pursuant to the Advisory Action of May 28, 2009.

V. Summary of the Claimed Subject Matter

Independent claim 1 is supported in the specification, for example, at page 1, line 24 to page 2, line 1, and page 17, lines 28-30.

VI. Grounds of Rejection to be Reviewed on Appeal

Grounds of rejection to be reviewed on appeal include the following:

Whether claims 1, 5, 7-9, 13, 15-17 and 22-26 obvious over Li *et al.* (1998; Exhibit 1) in view of Yamamoto *et al.* (1997; Exhibit 2) and Barker *et al.* (U.S. Patent 5, 851,775; Exhibit 3) as evidenced by Zrihan-Licht *et al.* (1994; Exhibit 4) under 35 U.S.C. §103. The argument against this rejection is presented below.

VII. Argument

A. Standard of Review

Findings of fact and conclusions of law by the U.S. Patent and Trademark Office must be made in accordance with the Administrative Procedure Act, 5 U.S.C. §706(A), (E), 1994. *Dickinson v. Zurko*, 527 U.S. 150, 158 (1999). Moreover, the Federal Circuit has held that findings of fact by the Board of Patent Appeals and Interferences must be supported by "substantial evidence" within the record. *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). In *In re Gartside*, the Federal Circuit stated that "the 'substantial evidence' standard asks whether a reasonable fact finder could have arrived at the agency's decision." *Id.* at 1312. Accordingly, it necessarily follows that an examiner's position on appeal must be supported by "substantial evidence" within the record in order to be upheld by the Board of Patent Appeals and Interferences.

B. Rejection Under 35 U.S.C. §103

Claims 1, 5, 7-9, 13, 15-17 and 22-26 are rejected as obvious over Li *et al.* (1998; Exhibit 1) in view of Yamamoto *et al.* (1997; Exhibit 2) and Barker *et al.* (U.S. Patent 5, 851,775; Exhibit 3) as evidenced by Zrihan-Licht *et al.* (1994; Exhibit 4). The examiner cites Li and Yamamoto as providing methods of identifying a compound that inhibits binding of the β-

catenin tumor progressor to a MUC1 test site. Barker is said to provide motivation for the use of a peptide fragment of β-catenin, and Zrihan-Licht is said to teach that the MUC1 test agent will necessarily be phosphorylated at the YEKV site. Appellant traverses.

i. The Examiner's Burden

In rejecting claims under 35 U.S.C. §103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a). In setting forth a *prima facie* case of obviousness, it is necessary to show "some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

ii. Appellants' Position

In the present case, there is *no prima* facie case of obviousness for the following reasons. Li teaches that glycogen synthase kinase 3β binds to an STDRSPYE site in MUC1 and phosphorylates the serine that is adjacent to the proline. This phosphorylation decreases the binding of MUC1 to β-catenin. Li does not teach or suggest that phosphorylation of a YEKV site increases binding of MUC1 to β-catenin. The examiner has cited to FIG. 5 of Li as teaching GSK3β as the test agent. However, there is no information in Li to teach or suggest that the test agent in Li was phosphorylated at a YEKV site. Nor would this be inherent, as it is possible for

a YEKV site to not be phosphorylated, and Li teaches that it is phosphorylation of a serine residue that affects interaction of MUC1 with β-catenin, not YEKV.

Yamamoto does not provide any teaching or suggestion concerning a MUC1 test agent phosphorylated at a YEKV site. Rather, it concerns certain studies demonstrating that DF3 (MUC1) binds directly to β-catenin and that the SXXXXXSSL motif in DF3 is responsible for this interaction.

Further, as admitted by the examiner, neither Li nor Yamamoto teach that the β-catenin test agent is a peptide fragment. Barker is cited as teaching that certain assays may be conducted utilizing a β-catenin fragment that is shorter than the full-length tumor progressor. It is not cited as providing any teaching or suggestion concerning assays concerning any MUC1 test agent, much less one that is phosphorylated at a YEKV site. The examiner admits that neither Li, Yamamoto, nor Barker teach that the MUC1 test agent includes a phosphorylated YEKV site. *See* Final Office Action, page 9.

While Zrihan-Licht discloses that MUC1 proteins are "extensively phosphorylated" and that phosphorylation occurs "primarily on tyrosine residues" (Abstract), it does not specifically teach phosphorylation of the YEKV site of MUC1. Indeed, the MUC1 protein includes 13 tyrosine residues, of which 7 are in the cytoplasmic domain, and there is no information in this reference or in any of the other references to suggest that the YEKV tyrosine residue, out of all of the amino acids of MUC1, is critical for binding to β-catenin. Further, Zrihan-Licht teaches that other residues may undergo phosphorylation, including serine residues. *See* p. 131, right col., third para. Still further, Zrihan-Licht teaches that the sequence YEEV is important for interaction with SH2 domain-containing tyrosine kinases, thus teaching away from the importance of a YEKV site. In addition, one of ordinary skill in the art would further be led

away from the importance of phosphorylation of a YEKV site because, as discussed above, Li teaches that it is a serine residue that affects interaction of MUC1 with β-catenin and Yamamoto teaches that the SXXXXXSSL motif in DF3 is responsible for this interaction.

Thus, it is again submitted that there is no *prima facie* case of obviousness based on the combination of references cited by the examiner. There is no rationale that would have led one of ordinary skill in the art, at the time of the invention, to believe that the YEKV site of MUC1 is critical for binding to β-catenin, and thus a critical target for screening.

iii. The Examiner's Rebuttal Fails

In the Advisory Action mailed on May 28, 2009, the examiner found the preceding line of argument unpersuasive, and offered the following points in rebuttal.

First, it was argued that appellants were improperly addressing the references individually, and not as a whole. This is incorrect. Appellants were pointing out specific defects in the references, and the incorrect nature of the examiner's assumptions therefrom. When viewed in light of these critical deficiencies, the references cannot, even when taken as a whole, suggest the present invention. This is because they neither individually ***nor collectively*** provide any evidence that the YEKV motif is integral to β-catenin's interaction with MUC1.

Second, turning to Li, the examiner argues that the reference teaches that tyrosine residues flank the identified β-catenin binding motif, and that modification of a serine residue near a YEKV tyrosine did not eliminate interaction with β-catenin. From this, the examiner finds that "Li neither teaches away, discredits or otherwise discourage[s] the ordinary artisan from determining the role tyrosine phosphorylation may play in the interaction between MUC-1 and β-catenin." This very statement highlights the improper nature of the rejection. The claimed invention is not a method of determining ***whether*** tyrosines generally play a role, but assessing

the effects of compounds on this action ***after*** it was determined that a specific tyrosine ***does*** play a role.

Third, the examiner makes a similar misapplication of the teachings of Yamamoto. As acknowledged, Yamamoto acknowledged that "it is not known if tyrosine sites influence binding of catenins to the serine rich motif." A more equivocal statement can hardly be imagined. Yet somehow, the examiner contorts this quote to into a "suggest[ion that] the phosphorylation of one or more of the seven tyrosine residues in the MUC1 cytoplasmic domain ... [is a] possible regulatory feature, wherein the YEKV site is immediately adjacent to the serine rich motif." To call this statement rank speculation would be too kind – it is nothing short of an outright misrepresentation of the teachings of the reference, as the previous quote from Yamamoto clearly disavows any evidence that tyrosines, much less YEKV tyrosines, are involved. The examiner, knowing this, hedges his bet by stating that "those of ordinary skill in the art were motivated to determine if other phosphorylated residues in the MUC1 cytoplasmic domain were responsible for the interaction between MUC1 and β-catenin." Again, appellants are ***not*** claiming to "determine" whether phosphorylated MUC1 residues have an impact on function, which this language would imply. Instead, they are claiming to exploit the finding, made by the inventors and ***not*** by Li or Yamamoto, that YEKV ***is*** in fact critical to MUC1's interaction with β-catenin. Without this knowledge, the prior art at best the art leaves one to pursue a general line of research that may or may not lead to fruition. This does not qualify as obvious. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Fourth, the examiner argues that appellants have overlooked the "emphasis" Zrihan "postulated" that MUC1 tyrosines interact with SH2 domain-containing proteins, while admitting that YEEV motifs are preferred. Thus, the examiner argues that "it does not teach

away from all other tyrosines." Whether or not this is true, it highlights the fact that Zrihan certainly does not ***suggest*** the significance of YEKV motifs, and ***that*** is what is being claimed here. Thus, this reference too lacks any reasonable teaching or inference that would guide the skilled artisan to YEKV. At most, this is an invitation to invent, and it certainly cannot obviate appellants' invention based on that alone.

In conclusion, appellants submit that the following summation, offered by the examiner, highlights the baseless nature of the rejection: "The tyrosine phosphorylation of MUC1, and the YEKV site in particular, ***necessarily flows*** from the signal transduction pathways in cancer cells of Li *et al.* (1998), Yamamoto *et al.* and Barker." This language smacks of a inherency theory, which has no basis in an obviousness rejection. The examiner is simply grasping at straws in an vain effort to support a rejection that lacks the required teaching, suggestion and motivation in the cited art. In the end, one of ordinary skill would have no reasonable expectation of success that phosphorylation of a YEKV site would be important for interaction with β-catenin. Therefore, the Examiner has not set forth a *prima facie* case of obviousness.

CONCLUSION

In light of the foregoing, appellants respectfully submit that all pending claims are non-obvious under 35 U.S.C. §103. Therefore, it is respectfully requested that the Board reverse the pending rejection.

Respectfully submitted,

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VIII. APPENDIX A – APPEALED CLAIMS

1. (Previously Presented) A method of identifying a compound that inhibits binding of MUC1 to a tumor progressor, the method comprising:

(a) providing a MUC1 test agent, wherein the MUC1 test agent comprises a phosphorylated YEKV site;

(b) providing a tumor progressor test agent that binds to the phosphorylated MUC1 test agent;

(c) contacting the phosphorylated MUC1 test agent with the tumor progressor test agent in the presence of a test compound; and

(d) determining whether the test compound inhibits binding of the phosphorylated MUC1 test agent to the tumor progressor test agent.

5. (Original) The method of claim 1, wherein the tumor progressor test agent is a β-catenin test agent.

7. (Original) The method of claim 1, wherein the contacting is carried out in a cell-free system.

8. (Original) The method of claim 1, wherein the contacting occurs in a cell.

9. (Previously Presented) The method of claim 1, wherein the test compound is a peptide fragment of the tumor progressor.

13. (Previously Presented) The method of claim 9, wherein the tumor progressor test agent is a β-catenin test agent.

15. (Previously Presented) The method of claim 9, wherein the contacting is carried out in a cell-free system.

16. (Previously Presented) The method of claim 9, wherein the contacting occurs in a cell.

17. (Previously Presented) The method of claim 1, wherein the MUC1 test agent comprises SEQ ID NO:1.

19. (Previously Presented) The method of claim 5, wherein the MUC1 test agent comprises SEQ ID NO:1 phosphorylated at Y46.

22. (Previously Presented) The method of claim 8, wherein the cell is a cancer cell.

23. (Previously Presented) The method of claim 22, wherein the cancer cell expresses MUC1.

24. (Previously Presented) The method of claim 22, wherein the cancer cell is a breast cancer cell, a lung cancer cell, a colon cancer cell, a pancreatic cancer cell, a renal cancer cell, a stomach cancer cell, a liver cancer cell, a bone cancer cell, a hematological cancer cell, a neural tissue cancer cell, a melanoma cell, an ovarian cancer cell, a testicular cancer cell, a prostate cancer cell, a cervical cancer cell, a vaginal cancer cell, or a bladder cancer cell.

25. (Previously Presented) The method of claim 5, wherein providing a phosphorylated MUC1 test agent comprises combining a MUC1 test agent, a tumor progressor test agent with kinase activity, and ATP, wherein a MUC1 test agent phosphorylated at a YEKV site is formed.

26. (Previously Presented) The method of claim 25, wherein the tumor progressor test agent with kinase activity is c-src, EGF-R, or PKCδ.

IX. APPENDIX B – EVIDENCE CITED

Exhibits 1-4 were previously submitted with our Appeal Brief dated August 25, 2009.

Exhibit 1 – Li *et al.* (1998)

Exhibit 2 – Yamamoto *et al.* (1997)

Exhibit 3 – Barker *et al.* (U.S. Patent 5,851,775)

Exhibit 4 – Zrihan-Licht *et al.* (1994)

X. APPENDIX C – RELATED PROCEEDINGS

None